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Reducing the Impact of Influenza Viral Load on Patient and Community Health

Dr. Doghramji: So take a moment to join me in picturing this all-to-familiar scenario. Waiting rooms are busting at the seams, the din of coughing is filling the air and phones are ringing off the hook. Yes, you guessed it, flu season is upon us once again. The good news is that this season we have more options to not only treat the flu, but also reduce the spread of illness from one patient to another. This newer option is not a neuraminidase inhibitor, but an endonuclease inhibitor and both work differently in their approach to reducing the viral load and the viral shedding of the flu virus.

This is CME on Reach MD and I am Dr. Paul Doghramji. Joining me today to discuss what we can effectively do to reduce the impact of viral load on the patient and community health in general is Dr. John Russell. Dr. John Russel is the Director of Family Medicine Residency at Abington Memorial Hospital in Abington, Pennsylvania. Dr. Russell, welcome to the program.

Dr. Russell: Paul, it's great to be with you today.

Dr. Doghramji: So John, we often hear these terms viral load and viral shedding, they are often used, but what are these terms, what is viral load and viral shedding in influenza and what role do they play in symptomatology and spread of the disease?

Dr. Russell: Paul, I think that's a great question and how I like to think about viral shedding, is how infectious I am to the public at large, right, so am I shedding virus in my respiratory epithelium and am I spreading that through coughing and sneezing. I think of viral load in terms of my personal disease burden of virus, so we think of viral load a lot with HIV infections and hepatitis C infections and I think as clinicians we are good at kind of wrapping our heads around people with more viral load have a large burden of disease and then when I think about viral shedding, I think of typhoid Mary. Typhoid Mary wasn't sick, but she shed infection. So I think it's a little bit of an external versus an internal. Now the window of duration of each is a little bit different, but they often mirror the same. So usually, I might be shedding influenza virus even before I get a fever, before I get sick in those days preceding and that might continue anywhere in that five to seven days and viral load at least for HIV often mirrors that. My viral load is highest in the beginning and decreases over that five to seven days.

Dr. Doghramji: Well great and thanks for breaking that down for us John in these two terms. And now that we know the difference between them, let's watch this brief video on the typical spread patterns for influenza and how we can potentially stop or limit the spread of the virus.

2D Animation:

Influenza is an acute respiratory illness that is caused by the influenza A or B viruses, that is primarily transmitted through both large droplets and small particle aerosols when an infected person coughs or sneezes, thus entering and working its way through the respiratory tract.

Once in the respiratory tract, it replicates and spreads throughout the respiratory system including the upper airways and lungs. As the replication of the virus continues it spreads throughout the rest of the body affecting the brain, heart, muscles, liver, kidney, eyes, and other organ systems (known as viral load), as well as leaving the host through the upper airways (known as viral shedding).

Upon receiving treatment with either baloxavir or with a more traditional neuraminidase inhibitor (such as oseltamivir), especially within

the first 48 hours of onset of symptoms, the viral load begins to diminish over the course of the next few days and viral shedding is also reduced.

As the infected person enters a crowded area, such as an airport, any cough or sneeze will release contaminated respiratory secretions into the environment.

These droplets and small particle aerosols will then enter via the upper airways of other individuals in both close proximity or in the general area due to the nature of the particles.

With a spread rate of 5% to 20%, numerous individuals will be exposed to the virus and will then disseminate the virus to other parts of the country and world.

Dr. Doghramji: So John, now that we know more about the typical spread patterns for influenza, does the severity of the illness say in an asymptomatic patient or one with mild illness versus those with more severe respiratory symptoms, have any impact on viral load or shedding?

Dr. Russell: So I think when you watch the video, that can be a little bit chilling, right, so you have someone chalk full of virus who is traveling through an airport, going all kinds of different things, going to school, going to daycare, going to the hospital, so people with a higher viral load and more viral shedding are out amongst us. So there can be some variances in the duration and volume of viral shedding, but we can't always know how much virus someone is actually shedding, but we can often know, who does that person live with and I think when I think of viral shedding, I don't always think of the index patient, I often think of who do they live with, who do they come in contact with and how can I prevent that person who I know has influenza, from getting other folks sick?

Dr. Doghramji: So John, returning to our conversation on the typical spread patterns for influenza, some studies have shown that it's typically around 10 to 20 percent of infected individuals who are responsible for 90 to 95 percent of the spread of infectious particles. Is there any way to identify and target these highly infectious individuals?

Dr. Russell: Boy it would be really terrific if we could identify the people who are going to spread influenza among our community like a scarlet letter, but in fact, we can't, and that's why it is very important for people to prevent influenza from happening by being vaccinated, but what we can identify is who are the populations at risk if they got influenza. So if someone worked at a nursing home and there was a lot of vulnerable people there, even though they have been vaccinated, well remember the vaccine does not work 100 percent of the time. It varies year to year and over the last 7 to 10 years we have been around that 40 percent range, so you could even have an infected individual around someone who has been vaccinated and they could get that individual sick. So we can't tell who is going to make people sick, but certainly when someone is sick, we can look at the people that they contact and perhaps even think about prophylaxing them against influenza, be it at home, office or nursing home.

Dr. Doghramji: Okay, and based on what you know about the mechanisms of action of both the neuraminidase inhibitors such as Oseltamivir and Endonuclease inhibitors such as Baloxavir, are there are differences you would anticipate seeing in terms of reductions in viral load or shedding?

Dr. Russell: So in you look in 2019, we have four different medicines that are available to us for treating influenza. We have three neuraminidase inhibitors. The neuraminidase inhibitors basically work by preventing the cell from releasing the influenza virus. We have one endonuclease inhibitor now, Baloxavir, which works on the production at an mRNA level of the influenza virus. Now when you look at the Capstone 1 trial, that looked at a lower risk population, and gave them Oseltamivir or Baloxavir, what they found that both classes of medicine, the neuraminidase inhibitor and the endonuclease inhibitor, made people better about a day shorter. When you looked at viral load, though, the Baloxavir had a marked decrease in viral load, about 24 hours, that took 72 hours for the Oseltamivir to obtain. Now what's the clinical significance of that? I think that is what we are talking about here today. But certainly there are papers and studies that are starting to come forward that are saying that if we do have a significant reduction in influenza viral replication, perhaps we will reduce influenza viral spread to close contacts and I think that's some of the things that need to be spread…. To be studied going forward.

Dr. Doghramji: Now there was some recent abstracts presented at the Options X, for the control of influenza conference in Singapore. Can you elaborate on some of the practical implications of these studies?

Dr. Russell: So there were several interesting studies that were looked at at that particular conference. Now the Blockstone study looked at Baloxavir within a household after you had an infected household member. So patients were randomized to either get placebo or Baloxavir. The results showed that roughly about 2 percent, 1.9 percent, of the Baloxavir treated household members developed flu versus 13.6 in the placebo group. This benefit remains statistically significant versus placebo regardless of the influenzae subtype, H1 N1, H3 N2. These results also applied to children under 12 years of age and high risk household members to decrease their chance of

developing flu. Now what we don't have in that study is Baloxavir versus Oseltamivir, which I think is a study that needs to be done to show how effective prophylaxis could be for high risk populations. Now some of the other studies that they talked about at this particular conference, they talked about Capstone 2 and in Capstone 2 you took a more high risk population and you compared Oseltamivir to Baloxavir and what they found, very similar to Capstone 1, is that Oseltamivir and Baloxavir both decreased in a higher risk population illness by about a day, but again it showed a decrease in viral load that happened much closer to one day with Baloxavir verses three days verses Oseltamivir. They also looked at the Ministone 2 trial. The Ministone 2 trial was much like the Capstone trials that looked at Baloxavir versus Oseltamivir in a population of children who were healthy between 1 and 12 years of age. What did it find? Well, what it found, much like our Capstone trials, that the Oseltamivir and Baloxavir both decreased illness by about the same amount of time, by about a day, but they found was the Baloxavir treated group had less adverse events from the medication than the Oseltamivir group and certainly those of us who have prescribed Oseltamivir certainly know that there can be some GI side effects for the folks who take it. If you are going to use Oseltamivir, sometimes giving that with some food in someone's belly can make Oseltamivir better tolerated. We might see soon that there might be a change in the age indication for Baloxavir, which at current is indicated for folks over the age of 12.

Dr. Doghramji: So logically it makes sense that treating patients with antivirals that have a rapid reduction in viral load will also reduce the duration of viral shedding. Now maybe this is the million dollar question, but is that truly the case?

Dr. Russell: So I truly think that is the million dollar question. So if we have two medicines that both have very similar efficacy, but one decreases viral load markedly quicker, one day versus three days, should we preferentially pick that medication? So there certainly have already been some studies, looked at Oseltamivir and by treating people earlier, there was far shorter periods of viral shedding. So I think we realize if we can start treatment earlier within 48 hours, we are going to have patients get a better response themselves to the medications and I think we are also going to see that people are going to spread it less to the people around them, but I think that is truly going to be the study that we are going to want to see, that if Baloxavir decreases viral shedding by about two days sooner than the Oseltamivir, how much does that impact the people on how… that we get infected from having influenza? Now if we look at the guidelines from 2018, from the Infectious Disease Society of America, it does say that we should start an antiviral for a patient admitted with influenza to the hospital. All of our patients, it doesn't really how long they have been sick. We should also consider our high risk population who have influenza starting treatment. In our lower risk population, we should start antivirals if we are seeing them within two days. For the rest of our population whose not at risk and we are seeing them beyond two days, it's not completely clear that antivirals will make a big difference for our outpatients.

Dr. Doghramji: Well this certainly has been a valuable discussion John and before we wrap up, what is one take home message you would like to leave with the audience today?

Dr. Russell: Well, I think a couple of points are one, the best case of influenza is the one that does not develop, so I certainly, with new medicines on the horizon, we shouldn't forget about getting people vaccinated. If we are going to treat someone with an antiviral with influenza, we should start it sooner. New guidelines that came out in December of 2018 say that all of our patients who are hospitalized with influenza should be treated and all of our high risk patients should be treated as well. Our lower risk patients if we are seeing them within two days, we certainly should consider treating them as well and it's nice we have new options for our patients.

Dr. Doghramji: Well, that's a great message for our audience to remember, as we wrap up the discussion today and would like to thank by guest, Dr. John Russell, for helping us better understand the spread of the flu virus within the community and how we can effectively treat it to reduce the viral shedding that occurs during the active illness. Dr. Russell, John, it was great speaking with you today.

Dr. Russell: Dr. Doghramji it was a real pleasure to be with you and talk about influenza treatments.